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| 09/986,797      | 11/13/2001  | Pascale Briand       | 03804.0101-02       | 6235             |

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| EXAMINER |
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CHEN, SHIN LIN

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| ART UNIT | PAPER NUMBER |
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1632

DATE MAILED: 01/13/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

**Office Action Summary**

Application N .

09/986,797

Applicant(s)

BRIAND ET AL.

Examiner

Shin-Lin Chen

Art Unit

1632

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

**Period for Reply**

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

**Status**

- 1) ☒ Responsive to communication(s) filed on 09 October 2003.
- 2a) ☐ This action is **FINAL**. 2b) ☒ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

**Disposition of Claims**

- 4) ☒ Claim(s) 14-26 is/are pending in the application.
- 4a) Of the above claim(s) \_\_\_\_\_ is/are withdrawn from consideration.
- 5) ☐ Claim(s) \_\_\_\_\_ is/are allowed.
- 6) ☒ Claim(s) 14-26 is/are rejected.
- 7) ☐ Claim(s) \_\_\_\_\_ is/are objected to.
- 8) ☐ Claim(s) \_\_\_\_\_ are subject to restriction and/or election requirement.

**Application Papers**

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on \_\_\_\_\_ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.
- Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
- Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

**Priority under 35 U.S.C. §§ 119 and 120**

- 12) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☐ All b) ☐ Some \* c) ☐ None of:
1. ☐ Certified copies of the priority documents have been received.
  2. ☐ Certified copies of the priority documents have been received in Application No. \_\_\_\_\_.
  3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).
- \* See the attached detailed Office action for a list of the certified copies not received.
- 13) ☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application) since a specific reference was included in the first sentence of the specification or in an Application Data Sheet. 37 CFR 1.78.
- a) ☐ The translation of the foreign language provisional application has been received.
- 14) ☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121 since a specific reference was included in the first sentence of the specification or in an Application Data Sheet. 37 CFR 1.78.

**Attachment(s)**

- 1) ☒ Notice of References Cited (PTO-892)
- 2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
- 3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) \_\_\_\_\_.
- 4) ☐ Interview Summary (PTO-413) Paper No(s). \_\_\_\_\_.
- 5) ☐ Notice of Informal Patent Application (PTO-152)
- 6) ☐ Other:

### **DETAILED ACTION**

1. Applicant's election with traverse of species, a defective recombinant adenovirus type 5 and administration via intravitreal injection, filed 10-9-03 is acknowledged. The traversal is on the ground(s) that there is no serious burden to examine all of the claimed species. This is not found persuasive because different adenoviruses have different host ranges and require different searches, therefore, there are serious burden for examiner to search for the full scope of the claimed species. However, the requirement for election of intravitreal injection or subretinal injection has been withdrawn.

The requirement is still deemed proper and is therefore made FINAL.

Claims 14-26 are pending and under consideration.

### ***Claim Objections***

2. Claims 19 and 25 are objected to because of the following informalities: The terms "RDS" and "NDI" in claim 19 and the term "MLP" in claim 25 are abbreviations and can represent various meanings. Spelling out the terms would be remedial. Appropriate correction is required.

### ***Claim Rejections - 35 USC § 112***

3. The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

4. Claims 14-26 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for expression of beta-galactosidase on the cells of the endothelial layer after anterior chamber injection of the adenovirus, expression of beta-galactosidase on the cells of point of intravitreal injection, and expression of beta-galactosidase on the fibers of the 4 oculomotor muscles after retrobulbar space injection, does not reasonably provide enablement for expressing a gene in at least an eye cell by using a defective recombinant adenovirus expressing a protein or an antisense RNA and expression of said gene via various administration routes could provide therapeutic effect in vivo for various eye disorders or diseases. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with these claims.

Claims 14-26 are directed to a method for expressing a gene in at least one eye cell comprising administering a defective recombinant adenovirus, such as adenovirus type 2 or type 5, expressing an inserted gene, which encodes a protein or an antisense RNA, to at least one eye cell in vitro or in vivo, wherein the defective recombinant adenovirus lacks either E1A or E1B region. Claims 18 and 19 specify the protein is growth factor, cytokine, neurotrophin, regulatory factor, ornithine aminotransferase, rhodopsin, basic fibroblast growth factor, interleukin-8 etc. Claims 22 and 23 specify the administration is subretinal injection or intravitreal injection. Claim 24 specifies the eye cell is corneal endothelium, photoreceptor cell, bipolar cell, ganglion cell, or oculomotor cell. Claim 25 specifies the sequence permitting expression of the gene is RSV promoter, E1A promoter, or MLP promoter.

The claims encompass administering a defective recombinant adenovirus expressing the gene encoding any protein or antisense RNA to at least an eye cell in vitro or in vivo via various

administration routes, including subretinal injection and intravitreal injection. The specification discloses expression of beta-galactosidase on the cells of the endothelial layer after anterior chamber injection of the adenovirus, expression of beta-galactosidase on the cells of point of intravitreal injection, and expression of beta-galactosidase on the fibers of the 4 oculomotor muscles after retrobulbar space injection (specification, p. 15-17).

The specification states "The present invention relates to new recombinant viruses, to their preparation and to their use in gene therapy for the transfer of genes to the eye and their expression therein. It also relates to pharmaceutical compositions comprising the said recombinant viruses. More especially, the present invention relates to defective recombinant viruses and to their use for the treatment of ocular pathologies" (specification, p. 1 lines 3-10). Expression of a gene in eye cells must have a use and the use is for gene therapy or treatment of ocular pathologies as indicated in the specification. Therefore, the claims are directed gene therapy in vivo. The specification fails to provide adequate guidance and evidence for how to use a defective recombinant adenovirus expressing a protein or an antisense RNA to treat an eye disease or disorder, such as ocular disease, via various administration routes so as to provide therapeutic effect in vivo. The specification also fails to provide adequate guidance and evidence for the correlation between the expressed protein or antisense RNA and a particular eye disease or disorder.

The nature of the invention being gene therapy, the state of the prior art was not well developed and was highly unpredictable at the time of filing. Verma (Sept. 1997, Nature, Vol. 389, pages 239-242) reports that "The Achilles heel of gene therapy is gene delivery, and this is the aspect that we will concentrate on here. Thus, far, the problem has been an inability to

deliver genes efficiently and to obtain sustained expression” (see page 239, right column). Verma also teaches appropriate regulatory elements may improve expression, but it is unpredictable what tissues such regulatory elements target (page 240, sentence bridging columns 2 and 3).

Further, Eck et al., 1996 (Goodman & Gilman’s The Pharmacological Basis of Therapeutics, McGraw-Hill, New York, p. 77-101) states that the fate of the DNA vector itself (volume of distribution, rate of clearance into the tissues, etc.), the *in vivo* consequences of altered gene expression and protein function, the fraction of vector taken up by the target cell population, the trafficking of the genetic material within cellular organelles, and the rate of degradation of the DNA, the level of mRNA produced, the stability of the mRNA produced, the amount and stability of the protein produced, and the protein’s compartmentalization within the cell, or its secretory fate, once produced are all important factors for a successful gene therapy (e.g. bridging pages 81-82). In addition, Gorecki, 2001 (Expert Opin. Emerging Drugs, 6(2): 187-198) reports that “the choice of vectors and delivery routes depends on the nature of the target cells and the required levels and stability of expression” for gene therapy, and obstacles to gene therapy *in vivo* include “the development of effective clinical products” and “the low levels and stability of expression and immune responses to vectors and/or gene products” (e.g. abstract). Administration route of a transgene to a subject plays an important role in determining the efficiency of gene transfer *in vivo*. In view of the reasons set forth above, one skilled in the art at the time of the invention would not know how to use a defective recombinant adenovirus expressing a protein or an antisense RNA to treat an eye disease or disorder, such as ocular disease, via various administration routes so as to provide therapeutic effect *in vivo*.

Claim 20 reads on using antisense RNA for gene therapy in vivo. Stein et al., 1993 (Science, Vol. 261, p. 1004-1012) states that the use of antisense oligonucleotide in the therapy of human disease must meet at least six criteria: "(i) the oligos can be synthesized easily and in bulk; (ii) the oligos must be stable in vivo; (iii) the oligos must be able to enter the target cells; (iv) the oligos must be retained by the target cell; (v) the oligos must be able to interact with their cellular targets; and (vi) the oligos should not interact in a non-sequence-specific manner" (e.g. abstract). Rojanasakul, Y., 1996 (Advanced Drug Delivery Reviews, Vol. 18, p. 115-131) reports that the effective use of antisense oligonucleotide for therapy has been limited due to several problems, such as naturally occurring oligonucleotides contain phosphodiester backbones that are easily degraded in a biological environment and therefore must be protected or modified to render stability, the antisense oligonucleotides are poorly taken up by cells and may not reach their target site, problems associated with cellular targeting, potential toxicity, and affinity of oligonucleotides to the target sites (e.g. abstract). Further, Branch, A., 1998 (TIBS, Vol. 23, p. 45-50) reports that antisense molecules and ribozymes are far more difficult to produce than was originally anticipated and their ability to eliminate the function of a single gene has never been proven, and there is a wide variety of unexpected non-antisense effects that make the use of antisense compounds as research agents more complicated (e.g. abstract). In view of the reasons set forth above, it would be unpredictable to express an antisense molecule in eye cells such that the expression of said antisense molecule could provide therapeutic effect in vivo.

For the reasons discussed above, it would have required undue experimentation for one skilled in the art at the time of the invention to practice over the full scope of the invention claimed. This is particularly true given the nature of the invention, the state of the prior art, the

breadth of the claims, the amount of experimentation necessary, the working examples provided and scarcity of guidance in the specification, and the unpredictable nature of the art.

***Claim Rejections - 35 USC § 103***

5. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negated by the manner in which the invention was made.

6. This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

7. Claims 14-17, 21 and 24-26 are rejected under 35 U.S.C. 103(a) as being unpatentable over Stratford-Perricaudet, et al., 1992 (J. Clin. Invest., Vol. 90, p. 626-630) in view of Tsai et al., 1992 (Arch. Ophthalmol., Vol. 110, p. 1167-1170).

Claims 14-17, 21 and 24-26 are directed to a method for expressing a gene in at least one eye cell comprising administering a defective recombinant adenovirus, such as adenovirus type 2 or type 5, expressing an inserted gene, which encodes a protein, to at least one eye cell in vitro or in vivo, wherein the defective recombinant adenovirus lacks either E1A or E1B region. Claim

24 specifies the eye cell is corneal endothelium, photoreceptor cell, bipolar cell, ganglion cell, or oculomotor cell. Claim 25 specifies the sequence permitting expression of the gene is RSV promoter, E1A promoter, or MLP promoter.

Stratford-Perricaudet teaches intravenously or intramuscularly administering a recombinant adenovirus 5, AdRSV $\beta$ gal, expressing beta-galactosidase under the control of RSV promoter to mice and shows less efficient expression of beta-galactosidase in adult mice as compared to neonatal mice via intravenous injection, and limited expression of beta-galactosidase on the point of injection via intramuscular injection, wherein the recombinant virus is replication incompetent due to its deletion of the E1 genes (e.g. p. 626 right column, p. 627). Stratford-Perricaudet also teaches the scope of somatic gene therapy goes beyond the treatment of muscle disease and direct introduction of purified nucleic acids into various organs in vivo is attractive due to its simplicity (e.g. p. 629).

Stratford-Perricaudet does not teach administering the replication incompetent adenovirus to eye cells.

Tsai teaches administering an adenovirus type 5 (Ad5) or adenovirus type 8 (Ad8) to corneas of cotton rats at a concentration of  $1 \times 10^5$  /mL and detects the presence of Ad5 or Ad8 in the ocular specimens isolated from the infected cotton rats (p. 1167, right column, table 2, p. 1170, right column).

It would have been obvious for one of ordinary skill in the art at the time of the invention to administer a defective recombinant adenovirus as taught by Stratford-perricaudet to eye cells as taught by Tsai because Stratford-Perricaudet teaches direct injection of the defective

recombinant adenovirus to various organs other than muscle for gene transfer and Tsai teaches administering Ad5 to corneas of cotton rat.

One having ordinary skill in the art at the time the invention was made would have been motivated to do so in order to determine the expression of beta-galactosidase in the administration site of the defective recombinant adenovirus as taught by Stratford-Perricaudet and Tsai with reasonable expectation of success.

***Conclusion***

No claim is allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Shin-Lin Chen whose telephone number is (703) 305-1678. Due to the move of USPTO to new site in Alexandria, Virginia, examiner's telephone number will be changed to (571) 272-0726 **after January 12, 2004**. The examiner can normally be reached on Monday to Friday from 9:30 am to 6 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Deborah Reynolds can be reached on (703) 305-4051. The fax phone number for this group is (703) 872-9306.

Any inquiry of a general nature or relating to the status of this application should be directed to the Group receptionist, whose telephone number is (703) 308-0196.



Shin-Lin Chen, Ph.D.